# Immunological Non Invasive Blood Tests to Evaluate Gastric Mucosa in Iraqi Dyspeptic Patients

**Batool M. Mahdi**


## ABSTRACT:

**BACKGROUND:**

Dyspepsia is a common symptom in general practitioner. Using non invasive serological biomarkers would help to identify individuals at increased risk of atrophic gastritis and gastric cancer. In present study, the evaluation of the utility of a serological gastric panel test combining pepsinogen I (PGI), pepsinogen II (PGII), pepsinogenI/ pepsinogenII ratio (I/II), gastrin-17 (G-17) (basal and stimulated) and Helicobacter pylori (HP) IgG antibodies as a screening method and to predict the state of gastric mucosa: non atrophic, atrophic gastritis and its sequel of developing gastric carcinoma and intestinal metaplasia.

**OBJECTIVE:**

Prediction of gastric mucosa using non invasive immunological blood tests from dyspeptic patients.

**PATIENTS AND METHODS:**

The serological gastro panel test was evaluated in (54) Iraqi dyspeptic patients divided into two groups: (HP +) and (HP-). Levels of PGI, PGII, PGI/PGII ratio, G-17 basal and stimulated and HP IgG antibodies were determined through a specific immunological non invasive Enzyme Linked Immuno Sorbent Assay (ELISA) test from Biohit PIC, Helsinki, Finland. Using fasting and postprandial samples from those patients.

**RESULTS:**

60% of dyspeptic patients complain from epigastric pain and 62.96% of them had HP +.There were significant increase in PGI, PGII ($p<0.05$) in NAG .In case of I/II ratio, there was no significant difference between two groups of HP+ and HP-.The other parameter was done is basal G-17 which is significantly increased in HP+ ($p>0.05$) and postprandial G-17 showed no significant difference between two groups.

**CONCLUSION:**

Most of those Iraqi dyspeptic patients had non atrophic gastritis due to *Helicobacter pylori* infection that leads to increased in the PGI, PGII, G-17 through many mechanisms. If HP not treated properly this may leads to atrophic gastritis , peptic ulcer and gastric carcinoma. Gastric panel test was considered as a non endoscope immunological blood test in the diagnosis of atrophic gastritis and its outcome in dyspeptic patients.


***KEY WARDS:*** helicobacter pylori, dyspepsia, gastro panel test.

## INTRODUCTION:

Dyspepsia (indigestion) is a collective term for non specific symptoms thought to originate from the upper gastrointestinal tract [(1)]. It is common in the general population, accounts about 8% of the consultations made with general practitioners, complaining from epigastric pain, early satiety, postprandial fullness, epigastric bloating, abdominal discomfort, somnolence, and nausea and vomiting [(2)]. These symptoms could be related to functional dyspepsia, gastro esophageal reflux disease, many gastrointestinal diseases (peptic ulcer and gastric neoplasm) and to other systematic diseases or ingestion of drugs like non steroidal anti-inflammatory drugs [(3)].

The general practitioner frequently suspects gastritis in patients with dyspepsia. The term GASTRITIS was used for a long time as a synonym for dyspeptic symptoms, but the term gastritis referred to pattern of injury and inflammatory infiltrations of gastric mucosa. Gastritis could not be diagnosed by medical examination or endoscope. It could be only diagnosed by histological analysis of gastric biopsy [(4)].

Dyspepsia is extremely prevalent and very often no abnormalities could be discovered during investigations. In 1982 the isolation of Helicobacter pylori (HP) by Barry Marshall and Robin Warren is a milestone in the aetiopathogenic

Department of Microbiology Al-Kindi College of Medicine.

comprehension of dyspepsia (gastritis, peptic ulcer, gastric cancer and gastric lymphoma [5]. In the industrialized world the prevalence of HP infection in the general population raises steadily with age and in underdeveloped world infection was much more common and often acquired in childhood [6].
HP related gastritis could have different histopathological patterns: non-atrophic gastritis (NAG) or called active superficial and atrophic gastritis (AG) or called active chronic whether in antrum or corpus of the stomach or both [7]. The persistence of AG could predispose to peptic ulceration or carcinoma and intestinal lymphoma [8].For this reason, the diagnosis of HP infection remains a subject of important interest in dyspeptic patients. Using a simple and economic immunological non invasive serological test was Sought to help the physician to screen patients with dyspepsia because isolation and identification of HP was difficult. According to Sipponen Scheme in 2001 [9], one can predict the state of gastric mucosa from these simple imuunological ELISA tests (HP Abs, PG I, PGII, I/II ratio and G-17 basal and stemulated) to suppose the state of gastric mucosa earlier to endoscpe and histological examination of biopsy.

## PATIENTS AND METHODS:

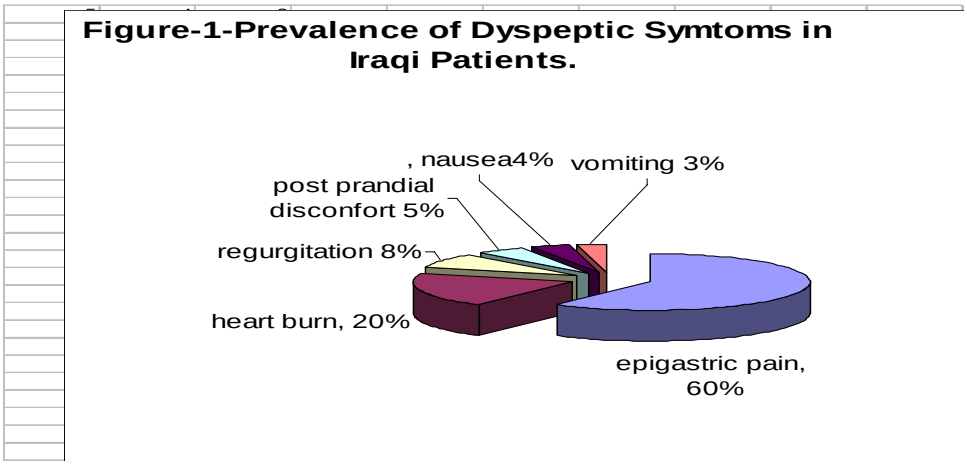
A total of fifty-four Iraqi dyspeptic patients were included in the present study who consulted my private clinic in the period between May 2005 to August 2008. Those with alarm symptoms were excluded like anaemia, melaena, haematemesis and dysphagia were excluded. Among them fourty were female and the rest were male. All of them were resided in Baghdad province was investigated by the Central Public Health Laboratory – Immunological Department in Baghdad.
Those patients were subjected to Gastro Panel test consisting of four parameters: Antibody to Gag A HP strain IgG Ab, PG I, PG II, I/II ratio and Gastrin-17 (basal and stimulated). At the beginning blood was sampled from ten hours fasting patients. Serum was separated and used for above tests (Enzyme Linked Immuno Sorbent Assay –ELISA- from Biohit PIC diagnostic, Helsinki, Finland. Then the patients were asked to eat about forty grams of protein about eight to twelve cubes of pure stick beef or lamb meat and after twenty to thirty minutes , venous blood was aspirated again and plasma was separated and stimulated Gastrin-17 was assessed by same above test .

## STATESTICAL ANALYSIS:

Data were presented as mean +/- standard error mean and statistical analysis were evaluated using student t-test.

## RESULTS:

A total of fifty-four Iraqi dyspeptic patients. Forty of them were female and the rest were male. Their age ranged from eighteen to sixty-two years old with a mean age of 35 years old.
Sixty of them were complaining from epigastric pain, 20% of them were suffered from heart burn and the rest postprandial discomfort, nausea, vomiting and regurgitation (Figure-1- ).



Those patients were subjected to Gastro Panel test, as shown in (Table-1-) 62.96% were HP + which is significantly difference from HP- (<0.05).

**Table 1: Prevalence of HP IgG Abs in Iraqi Dyspeptic Patients.**

| Title | HP+ IgG >38EIU | HP- IgG <38EIU | Total |
|---|---|---|---|
| Number of patients | 34 * | 20 | 54 |
| % of patients | 62.96 * | 37.03 | 99.99 |

* p<0.05 ( Normal value<38 EIU)

Estimated PGI in HP + patients was significantly increased in comparison with HP- patients (p<0.05) (table-2- ).

**Table 2: Number and Percentages of PGI in HP+ and HP- Iraqi Dyspeptic Patients.**

| Title | HP+ patients No. | % | HP- patients No. | % |
|---|---|---|---|---|
| PGI >150 µg/L | 14 (1) | 41.17 | 2 | 10 |
| PGI<50 µg/L | 9 (2) | 26.47 | 4 | 20 |
| PGI (50-150) µg/L | 11 (3) | 32.35 | 14 | 70 |
| Total | 34 | | 20 | |

(1), (3): p<0.05 (2): not significance.

When comparing serum PG II in HP + (58.82%) with HP – (25%), there was a significant difference (p<0.05) between them as shown in Table-3-.

**Table 3: Number and Percentages of PGII in HP+ and HP- Iraqi Dyspeptic Patients.**

| Title | HP+ patients No. | % | HP- patients No. | % |
|---|---|---|---|---|
| PGII >10 µg/L | 20 (1) | 58.82 | 5 | 25 |
| PGII<3 µg/L | 8 (2) | 23.52 | 4 | 20 |
| PGII (3-10) µg/L | 6 (3) | 17.64 | 11 | 55 |
| Total | 34 | | 20 | |

(1), (3): p<0.05 (2): not significance.

In case of PG I/PG II ratio as demonstrated in Table-4-, there was no significant differences between two groups.

**Table 4: Number and Percentages of PGI/PGII Ratio in HP+ and HP- Iraqi Dyspeptic Patients.**

| Title | HP+ patients No. | % | HP- patients No. | % |
|---|---|---|---|---|
| PGII/PGII>20 | 4 (1) | 11.76 | 3 | 15 |
| PGI/PGGII<3 | 10 (1) | 29.41 | 2 | 10 |
| PGI/PGII(3-20) | 20 (1) | 58.82 | 15 | 75 |
| Total | 34 | | 20 | |

(1): not significance.

When measuring gastrin-17 in fasting state and after protein ingestion, we found that there was significant increase in basalG-17 in HP+(23.35) with HP- (65%) ($p>0.05$). While stimulated G-17 there was no significant differences between two groups as demonstrated in Tables -5,6-.

**Table 5:Number and Percentages of Gastrin-17 (basal) in HP+ and HP- Iraqi Dyspeptic Patients**.

| Title | HP+ patients No. | % | HP- patients No. | % |
|---|---|---|---|---|
| Basal G-17>10 pmol/L | 11 | 23.35 (1) | 13 | 65 |
| basalG-17<2 pmol/L | 6 | 17.64 (2) | 3 | 15 |
| BasalG-17(2-10) pmol/L | 17 | 50 (3) | 4 | 20 |
| Total | 34 | | 20 | |

(1), (3): $p>0.05$ (2): not significance.

**Table 6:Number and Percentages of Gastrin-17(stimulated) in HP+ and HP- Iraqi Dyspeptic Patients.**

| Title | HP+ patients No. | % | HP- patients No. | % |
|---|---|---|---|---|
| Stimulated G-17>30 pmol/L | 27 | 79.41 (1) | 15 | 75 |
| Stimulated G-17<5 pmol/L | 4 | 11.76 (1) | 3 | 15 |
| Stimulated G-17 (5-30) pmol/L | 3 | 8.82 (1) | 2 | 10 |
| Total | 34 | | 20 | |

(1): not significance.

This study showed that non-invasive Gastric panel results can predict different patterns of gastritis and its sequel in Iraqi dyspeptic patients as demonstrated in Table-7- below.

**Table 7: Pattern of Gastritis and its sequel in abnormal Gastric Panel test.**

| Pattern of gastritis | HP+ patients No. | % | HP- patients No. | % | Sequel |
|---|---|---|---|---|---|
| Non atrophic gastritis | 25 | 73.52 (1) | 14 | 70 | ↑risk of DU |
| Antrum atrophy | 2 | 5.88 (1) | 2 | 10 | ↑risk of DU GU,GC%18 |
| Corpus atrophy | 5 | 14.7 (1) | 3 | 15 | ↑risk of GC%5 |
| Diffuse atrophy | 2 | 5.88 (1) | 1 | 5 | ↑risk of GC %90 |
| Total | 34 | | 20 | | |

(1): not significance

In non atrophic gastritis with HP+, there was significant increased in the level of PGI and PGII ($p>0.001$) in judge against HP- patients while other parameters were significantly decreased as revealed in Table-8-.

**Table 8: Mean ± SEM of non atrophic gastritis (NAG) in both HP+ and HP- Dyspeptic Iraqi Patients.**

| Title | HP+ patients NAG No.=25 $\bar{X}$ ± SEM | HP- patients NAG No.=14 $\bar{X}$ ± SEM |
|---|---|---|
| PGI (50-150) µg/L | 138.66 ± 1.4 (1) | 106.95 ± 1.53 |
| PGII (3-10) µg/L | 20.26 ± 0.6 (2) | 14.14 ± 0.9 |
| PGI/PGII(3-20) | 10.2 ± 0.8 (3) | 14.09 ± 0.9 |
| BasalG-17(2-10) pmol/L | 10.5 ± 0.7 (4) | 45.38 ± 1.4 |
| Stimulated G-17 (5-30) pmol/L | 89.3 ± 1.4 (5) | 102.66 ± 2.7 |

(1), (2), (4): $p>0.001$ (3): $p<0.05$
(5): $p<0.01$

The last table explained that there were significant decrease in the level of PGI and stimulated level of G-17 in HP+ in ($p<0.01$) in relation with HP-.that had atrophic gastritis. In case of PGII, there was significant increase in its level in HP+ with AG ($p<0.01$) (Table-9- ).

**Table 9: Mean ± SEM of atrophic gastritis (AG) in both HP+**

| Title | HP+ patients AG No.=9 $\bar{X}$ ± SEM | HP- patients AG No.=6 $\bar{X}$ ± SEM |
|---|---|---|
| PGI (50-150) µg/L | 32.69 ± 1.06 (1) | 41.96 ± 2.3 |
| PGII (3-10) µg/L | 11.3 ± 1.1 (2) | 5.73 ± 1.01 |
| PGI/PGII(3-20) | 17.8 ± 1.7 (3) | 13.3 ± 1.3 |
| BasalG-17(2-10) pmol/L | 8.2 ± 0.9 (4) | 4.5 ± 1.01 |
| Stimulated G-17 (5-30) pmol/L | 27.8 ± 2.7 (5) | 53.26 ± 4.4 |

(1), (2), (5): $p<0.01$ (3)(4):not significance

And HP-Dyspeptic Iraqi Patients.

## DISCUSSION:

Little is known about how many dyspeptic individuals in the population who consult medical and non-medical practitioners for their different symptoms. In our study about 60% of dyspeptic patients complaining from epigastric pain and 20% of heart burn which is in agreement with other reports[10].

Strategies based on screening for Helicobacter pylori in those dyspeptic patients in primary care have been proposed using Gastro Panel test. We noticed the presence of IgG Abs to Gag A Hp strain in the serum of Iraqi dyspeptic patients, this Cag A protein induced changes in host cellular protein and contribute in the inflammation of gastric mucosa by secretion of IL-8 and neutrophil activating protein that recruit neutrophils to gastric mucosa [11], thus Hp constitute 62.96% as a causative agent for dyspepsia which is significantly difference ($p<0.05$) from Hp IgG negative patients (37.03%). Our results were compatible with other studies that showed a significant relationship between Hp and dyspepsia [12].

This study showed that Hp induced significant increased in PGI and PGII levels in the serum and according to Siphoned 2001 indicate non atrophic gastritis of gastric mucosa. This results was similar to Kang *etal* 2008 [13] results and to other reports [14, 15].Levels of PGs were influenced by the physiopathologic status of gastric mucosa [16].Increased in PGI in HP + was due to cytotoxic

type of this strain of bacteria and used as a marker for peptic ulcers [17].While decreased in the level of PGI indicate corpus atrophy.

Regarding PGII, our results showed significant ncreased in PGII levels in HP+ compared to HP- group. This is because PGII produced by the whole stomach [18] and independently of the topography of gastric inflammation [19].So any increase in the expansion of gastritis before the development of atrophy causes replacement of chief cells by pyloric glands causing increasing in PGII [20]. Our results were in agreement with Miki and Urita results in 2007 [21]. Thus HP increased PG secretion from human peptic cells through a calcium and nitric oxide mediated intracellular pathway and may be a mechanism of induced gastric mucosal damage [22],so PG had been used as a biomarkers of gastric inflammation and mucosal status , thus decreased in its level indicate atrophy in the corpus of gastric mucosa. It was used as a first screening step and serologic biopsy in Japan for high risk subjects with gastritis.

Our results showed that PGI/PGII ratio did not significantly difference between HP+ and HP- groups which is differ from other results because most of our patients had non atrophic gastritis while in other reports showed atrophic gastritis in the gastric mucosa due to HP infection, so it was used as an index of gastric atrophy when it was decreased and decreased linearly with increasing grade of atrophic gastritis[23].It had been shown that the risk of gastric cancer was increased five fold when PGI/PGII ratio is low[24].

These changes are an indication of the histopathological state of the gastric mucosa and correlate with a degree of gastric atrophy in HP infected gastric mucosa [25].

The antral hormone gastrin that secreted from G-cells regulates gastric acid secretion and growth of gastric mucosa, the predominant form was Gastrin -17 that found in the serum and plasma [26, 27]. Basal G-17 was significantly increased in HP+ in relation with HP- group, this is due to HP stimulate and induce antral G-cells hyper function as a compensatory mechanism resulting in increased gastrin synthesis and degranulation of gastrin producing cells [28] and Gastrin was capable of up-regulation of chemokines in gastric epithelial cells[29].In addition, HP enhance apoptosis and transient cell cycle events leading to epithelial cells proliferation and increasing gastrin secretion due to increased cytoplasmic cell granule index of antral G-cells [30,31,32].Others found that HP enhanced activity of (PAF) (platelets activating factor) and higher expression of NF-Kappa B, this PAF induce influx of extra cellular of calcium via L-type channels and activation of protein kinase [33,34].

Basal G-17 was significantly higher in HP+ patients compared to HP- group which is in agreement with other reports [35, 36].

After eating few cubes of pure meat and measuring stimulated G-17, our results showed increased in stimulated G-17 in HP+ and it's no significant difference with HP- group (table-6- ). Other reports showed increased in stimulated G-17in HP+ [37] which is in agreement with our results while in patients with antral atrophy showed decreased in S-G17 in HP+after excluding factors causing hyperchlorhydria [38]. Decreased antral D cells number might be one of the reasons for hypergastrinemia [32].

According to Sipponen scheme in 2001(9) , one can predict that most of our dyspeptic patients had NAG (37.52%) that had abnormal gastric panel test which is significantly difference from HP-ve group (Table 8) and the rest had atrophy in corpus or antrum or diffuse and one can predict its sequel of increased risk of peptic ulcer and gastric carcinoma (Table-7-).Our results in agreement with Pimenov and Makarenko 2008 [39] and Storskrubb etal 2008 [40] that immunological serum markers provide an accurate method for diagnosis atrophic gastritis in general population instead of invasive gastroscope method . If this NAG did not treated may end in AG and PU and finally GC. In addition to that dementia, polyneuropathy and heart attacks and strok may results due to maleabsorbtion to vitamin B12 and consequent abnormalities in the metabolism of homocysteine and methoionin in extragastric tissues and cells [41].

**RECOMMENDATION:**

Most of our Iraqi patients refused endoscope and biopsy to detect gastric ulcer,HP presentation and to do histopathology .So

we recommended that every patient with dyspepsia who ask an outpatient or consultation clinic do this immunological non invasive test to predict the state of his gastric mucosa and the presence of HG infection and treat him accordingly.

**CONCLUSION:**

Most of those Iraqi dyspeptic patients had non atrophic gastritis due to *Helicobacter pylori* infection that leads to increased in the PGI, PGII, G-17 through many mechanisms. If HP not treated properly this may leads to atrophic gastritis , peptic ulcer and gastric carcinoma. Gastric panel test was considered as a non endoscope immunological blood test in the diagnosis of atrophic gastritis and its outcome in dyspeptic patients.

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**284**